Managing Myeloma

Key ASH Takeaways, Plus Daratumumab in the Relapsed/Refractory Setting

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Welcome to *Managing Myeloma*. I am Dr. Sagar Lonial, and I am live at the ASH Annual Meeting in Atlanta, Georgia. Today, I will be reviewing a trial evaluating the combination of daratumumab with carfilzomib and dexamethasone in patients with relapsed and refractory myeloma (Abstract 1869). This is a trial that was really trying to look at a combination that had not been explored before. We know from large phase 2 or phase 3 trials that daratumumab can be combined with lenalidomide, pomalidomide, or bortezomib, but had not yet been combined with carfilzomib. This was a nice proof of concept trial combining carfilzomib with daratumumab and dexamethasone. A unique aspect of this trial was not only the combination, but the fact that carfilzomib was given on a once-a-week schedule at a dose of 70 mg/m^2. What we demonstrated in this trial was an overall response rate of about 86% in all patients, and a response rate of about 81% among patients who were lenalidomide refractory. The progression-free survival (PFS) at 12 months was over 70% for patients in aggregate, suggesting that not only was this a highly active regimen, but that the durability of this combination was quite good. In terms of adverse events, they were not different from what one might expect in a daratumumab-based trial. Infusion reactions were at low incidence in the first two doses of treatment, and almost non-existent beyond treatment two of daratumumab and what has been reported for 70 mg/m^2 weekly of carfilzomib. I think it is really an important study, and one of the questions that is currently ongoing in the myeloma community is "What is the better partner for daratumumab? Is it a proteasome inhibitor (PI) or an immunomodulatory drug (IMiD)?" There is a lot of data suggesting that IMiDs are synergistic when combined with an antibody, but this study is part of the growing amount of evidence that suggests a PI may also be synergistic with daratumumab. This is really important because for patients who are PI sensitive or IMiD refractory, this combination may be very useful in clinical practice today.

We are going to talk today about the final results of the GEN501 and SIRIUS studies that were presented at ASH this year. One of the things that is really important was that this was the final analysis of the pooled treatment between these two studies; the phase 1 trial with the expansion cohort, as well as the phase 2 SIRIUS study that led to the FDA approval of daratumumab in the United States. This yielded a total of over 140 patients with a median follow-up of about three years. What was quite exciting about this study is that the responses, again, continue to be about 30% in aggregate for the trial, but with longer follow-up, no new adverse events or new toxicities were noted in the entire treatment cohort of patients. More importantly, in a refractory myeloma patient population, one-third of these patients remained alive at three years follow-up. What this update gives us information on is the fact that daratumumab as a single agent is well-tolerated, it can be effective in relapsed and refractory myeloma, and that there were no new side effects seen with prolonged therapy. In fact, in subsets of patients, not only could progression-free survival (PFS) be quite good, but actually overall survival was better than what you would expect from historical controls.

What we are going to talk about in this installment is that the treatment landscape for multiple myeloma continues to expand with many new drugs and combinations. One of the important educational messages that comes out at ASH is the idea that early relapse is the *new* newly diagnosed myeloma. What I mean by that is our concepts have been to treat very aggressively early on, to try and maximize depth of response. What we have seen from phase 3 updates at this meeting is that patients who have good depth of response with MRD negativity or overall high response rates and CR rates in the early salvage setting actually have prolonged progression-free and overall survival. What this means is the idea of using sequential single agents as salvage is probably gone in myeloma. Triplets are the ruling approach for the day, even in early relapse, and this approach can result in longer PFS and overall survival.

What I want to spend just a moment talking about are some of the potential practice-changing trials that may be coming out in 2018. I think that probably one of the most exciting areas for all of us is the area of CAR-T cells. What we hopefully will begin to see is larger patient populations, or phase 2 expansions of some of those phase 1 studies that have looked so encouraging. We may also begin to see other antibody-drug conjugates (ADCs) with monoclonal antibodies. We have again seen updates of the phase 1 trial at ASH 2017, and we are looking forward to potentially phase 2 data on that same target as well. Finally, we will continue to watch the many other molecularly targeted trials, as well as updates from some of those smoldering trials where the activity looks very good, but long-term outcomes are probably the important question. There is a lot on the plate in 2018, and stay tuned for additional updates in myeloma. Thank you very much for viewing this activity.

References:

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